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Title: TREATMENT OF DISEASE
EMPLOYING HYALURONIC ACID
AND NSAIDS

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OCT 31 1997

Examiner: DR. KATHLEEN FONDA

Group Art Unit: 1211

Due Date: July 16, 1996

The Commissioner of Patents
UNITED STATES PATENT OFFICE
2011 Jefferson Davis Highway
Crystal Plaza 2, Room 1B03
Arlington, Virginia
U.S.A. 22202

DECLARATION OF GEORGE A. DEVEBER
under §1.132

I, GEORGE A. DEVEBER, make oath and say as follows:

1. I am a Medical Doctor qualified in general internal medicine (FRCP) (C) and a practicing nephrologist for in excess of 30 years now, certified by the American Board

of Internal Medicine. I obtained my medical undergraduate degree from the University of Toronto.

2. Now shown to me and marked as Exhibits A and B to this my Declaration is a copy of my Curriculum Vitae and Bibliography respectively.

3. I am a Medical Consultant to the Assignee, Hyal Pharmaceutical Corporation, of U.S. Patent Application Serial No. 07/675,908 which is, I am advised by Ivor Hughes, Counsel to Hyal Pharmaceutical Corporation, the National Entry Application into the United States from PCT International Publication No. WO 91/04058 filed September 18, 1990.

4. As a Medical Consultant, I was involved in advising Hyal Pharmaceutical Corporation and have carried out research and development and ^{Dr. A. E. V.} ~~testing~~ for Hyal Pharmaceutical Corporation. I would not, however, let my acting as a Consultant for Hyal Pharmaceutical Corporation or for anyone, interfere with or cloud my professional objectivity and responsibilities in preparing any declaration.

5. I consider myself to have in-depth knowledge of the products of Hyal and their use and application. These products include forms of hyaluronic acid for example, sodium hyaluronate having various molecular weights, amounts and percentage concentrations. I have, as well, written confidential articles with respect to the medical applications and uses of hyaluronic acid. These articles are kept on file at Hyal Pharmaceutical Corporation's offices.

6. I have read the application 07/838,675 and as a medical doctor I would have no troubles from the teachings of this application determining the appropriate


dosage amounts given the fact that I know from the examples that the formulations containing between 1% and 3% hyaluronic and 1% and 5% NSAID are effective to treat and resolve basal cell carcinoma and the fact that accumulation of the composition in the epidermis of the skin is taught in the application. This accumulation is shown in the tests at pages 28-33 and pages 49-51 of the application. The blood levels test at pages 49-51 shows that the formulation does not enter the blood and thus would be accumulated in the skin and discharged through the lymphatic system. It would be easy for me to conduct tests on a limited number of individuals having basal cell carcinoma or arrange for tests to be conducted on individuals having basal cell carcinoma using various amounts of the formulations taught in the application to determine optimal dosage amounts. These tests would require minimum effort and not constitute experimentation as I am already aware that the administration of the formulations resolves the basal cell carcinoma. The application specifies several dosages (for example, 20 mg/cm² of the form of hyaluronic acid and 2 grams of the formulation). I would start with these formulations in my tests to determine optimal dosages that I would prescribe.

7. I would also have no trouble specifying the period of time and number of applications daily for the use of such formulation. Persons skilled in the art would understand these expressions. The phrases are ordinary English and such persons would know to prescribe the use of the formulations a number of times daily over a period of time sufficient to clear and resolve the basal cell carcinoma. The patent application specifically teaches through its examples that the basal cell carcinoma is cleared using the formulations. Persons skilled in the art would have no difficulty understanding these expressions with respect to the method of treatment. Finally, with respect to the expression "molecular weight", persons skilled in the art would have no trouble understanding the expression "molecular weight" and what is

suitable to be used. The molecular weights of the amounts of hyaluronan used also refer to the supplier who can be easily contacted for information if required. No misunderstanding is created by the expression "molecular weight".

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements will jeopardize the validity of the application and any patent issuing thereon.

EXECUTED this 10th day
of October, 1996.



GEORGE A. DEVEBER (M.D. FREQU)

EXHIBIT A

CURRICULUM VITAE

SUMMARY

1. Experienced physician with extensive background in hospital, corporate and academic fields, including managerial and executive roles. Has developed key networking contacts throughout the healthcare, government, biotechnology and academic communities. Skilled in project management, staff recruitment and development. Current activities include Medical Director of Hyal Pharmaceutical Corporation, Vasogen Inc. and provision of consulting services to Baxter Corporation and Hyal Pharmaceutical Corporation.

EXPERIENCE - ACHIEVEMENTS

2. **HYAL PHARMACEUTICAL CORPORATION** Jan. 1, 1994-present
Medical Director
 - (a) Responsibility in respect of clinical trials with respect to formulations using hyaluronic acid (sodium hyaluronate) alone or in conjunction with medicines for example the NSAID diclofenac;
 - (b) Wrote internal corporate review of Biology, Pharmacology clinical trials and potential applications of compositions containing hyaluronic acid (sodium hyaluronate).
3. **VASOGEN INC.** 1994-present
Medical Director
 - (a) Responsible for clinical development, clinical trials and regulatory affairs.
4. **BAXTER CORPORATION** 1987-1992
Vice-President Medical Affairs
 - (a) Worked mainly with specialty product divisions, such as renal and cardiovascular, where end user influence is strong;
 - (b) Provided medical/scientific support regarding marketing, educational programs;

- (c) Provided medical liaison and support to Baxter's Canadian regulatory group with respect to new product submissions, clinical trials; dealt directly with Health Protection Branch (Canada);
- (d) Assisted in designing and monitoring several clinical trials in Canada;
- (e) Responsible for external biotechnology assessment and transfer.

5. **TORONTO WESTERN HOSPITAL**

1965-1987

(i) **Director, Division of Nephrology, 1972-1987**

- (a) Developed an internationally recognized academic nephrology division with a full range of clinical, teaching and research programs;
- (b) Recruited five additional geographic full-time staff each of whom developed international reputations in clinical and/or basic research. Three of them are recognized as having made major therapeutic advances in haemodialysis, peritoneal dialysis, and renal transplantation;
- (c) Created an environment in which everyone involved in the program, including allied services (nursing, laboratories, social services, etc.) functioned as a team whose goals were to provide optimal patient care in an atmosphere which fostered research and education;
- (d) Developed an internationally recognized training program in Nephrology;
- (e) Carried out all the usual functions of an academic physician including undergraduate and postgraduate teaching as well as serving on multiple departmental, hospital and university committees.

(ii) **Director, Dialysis and Transplantation Program, 1965-1972**

- (a) Started Ontario's first formal dialysis and renal transplantation program which by 1987 had developed into one of Canada's 1,000 renal transplants performed;

(b) In connection with the program, initiated the following external support functions:

- The Ontario Branch of the Kidney Foundation of Canada
- The first transplant organ sharing network in Ontario
- The organ donor publicity program including having a consent form placed on the driver's license.

6. POST GRADUATE AND SPECIALTY TRAINING

1957-1965

1962-1965 Subspecialty Training in Nephrology -
Methodist Hospital,
Houston, Texas

1960-1962 Internal Medicine and Pathology -
Royal Victoria Hospital,
Montreal, Quebec

1958-1959 General Practice -
Sudbury and Cambridge, Ontario

1957-1958 Internal Medicine -
Shaughnessy DVA Hospital,
Vancouver, B.C.

7. EDUCATION AND SPECIALTY QUALIFICATIONS

1956 M.D. - University of Toronto

1963 Fellow - Royal College of Physicians
and Surgeons of Canada

1964 Diplomate - American Board of
Internal Medicine

8. PROFESSIONAL APPOINTMENTS

1983-1985 President, Kidney Foundation of Canada
(Ontario Branch)

- 1982-1983 President, Canadian Transplantation Society
- 1980-1984 Co-ordinator, Undergraduate Clinical
Methods Teaching,
Toronto Western Hospital, Toronto
- 1980-1984 Chairman, Medical Education Committee,
Department of Medicine,
Toronto Western Hospital, Toronto
- 1974-1975 President, Medical Staff Association,
Toronto Western Hospital, Toronto
- 1972 Associate Professor, Department of Medicine,
University of Toronto
- 1970-1974 Co-ordinator, Postgraduate Nephrology Training Program,
University of Toronto

9. **MEMBERSHIPS**

- 1981 Member, Canadian Transplantation Society (Founding)
- 1977 Member, Canadian Society for Immunology
- 1975 Member, American Society of Transplant Surgeons & Physicians
- 1972 Member, International Society of Nephrology
- 1970 Member, American Society of Artificial and Internal Organs
- 1969 Member, International Transplantation Society
- 1967 Member, Canadian Society of Nephrology (Founding)
- 1966 Member, American Society of Nephrology

10. **AWARDS**

- 1991 Initial recipient of Kidney Foundation
(Ontario Branch) Annual Distinguished Service Award
(created in my name)

1990 David Ornstein National Distinguished Service Award
Kidney Foundation of Canada

1966 Best Clinical Teacher, Department of Medicine
Toronto Western Hospital

EXHIBIT B

BIBLIOGRAPHY-GEORGE A. DEVEBER

1. Glomerulonephritis. Editorial. Canada Med. Assoc. J. 94: 144-145 (1966)
2. Fluid and Electrolyte Problems in the Postoperative Period. Nursing Clinics of North America: 275-284 (1966)
3. Cyclophosphamide Therapy in Adult Glomerulonephritis. Laval Med. 39: (1968)
4. Effect of Haemodialysis on Thyroid Function. deVeber, G.A. and Schatz, D.L. Proc. European Dialysis & Transplant Ass. 226-229(1968)
5. Influence of Heparin on Serum free Thyroxine. Schatz, D.L., Sheppard, R.H., Steiner, G., Chanderlapaty, C.S. and deVeber, G.A., J. Clin. Endocrinol. 29: 1015 (1969)
6. External Arteriovenous Shunts for Haemodialysis: A Technique for Insertion and the Importance of Venous Resistance. Williams, W.C. and deVeber, G.A. Canadian J. Surg. 12: 302-309 (1969)
7. Management of Acute Rejection in Heart Transplants. deVeber, G.A. Laval Med. 41: 1970. Presented at Second World Symposium on Heart Transplantation, Montreal, June, 1969.
8. Changing Pattern of Renal Osteodystrophy with Chronic Haemodialysis. deVeber, G.A. et al. Trans. Amer. Soc. Art. Intern. Organs, 16: 479-485 (1970)
9. Idiopathic Focal Proliferative Glomerulonephritis Associated with Persistent Haematuria and Normal Renal Function. Rapoport, A., Davidson, D.A., deVeber, G.A., Ranking, G.N. and McLean, C.R. Ann. Intern. Med. 73: 921-928 (1970)
10. Plasma-Calitonin in Renal Osteodystrophy. Chittai, S.M., Oreopoulos, D.G., deVeber, G.A., Thomas, P., Rabinovich, S., Lloyd, G.J., Kumar, M.A. & Rapoport, A. C.M.A.J., June 19, 1971, Vol. 104
11. A Study of Cell-mediated Immunity to Transplantation Antigens in Human Renal Allograft Recipients. Falk, R.E., Guttman, R.D., Falk, J.A., deVeber, G.A., Wilson, D.R., Beaudoin, J.G. & Morehouse, D.D.. Transplantation Proceedings, Vol. IV, No. 2, June, (1972)
12. Excretion and Metabolism of Reserpine in Renal Failure. Zsoter, T.T., Johnson, G., deVeber, G.A. & Paul, H. Clinical Pharmacology & Therapeutics, Vol. 14, No. 3, pp. 325-330, May - June, (1973)
13. Use of the Deane Prosthesis in Patients on Long Term Peritoneal Dialysis. Bigelow, P., Oreopoulos, D. & deVeber, G.A. C.M.A.J. Vol. 109, Nov. 17, (1973)
14. Contrasting Bone Changes in Patients on Chronic Haemodialysis and Chronic Peritoneal Dialysis. Oreopoulos, D., Rabinovich, S., Meema, H., Lloyd, G.J., Rapoport, A. & deVeber, G.A. Clinical Aspects of Metabolic Bone Disease (1973)
15. Contrasting Effects of Haemodialysis and Peritoneal Dialysis on Inhibition of In Vitro Calcification by Uremic Serum. Oreopoulos, D., Pitel, S., Hsuan, H., deVeber, G.A. & Rapoport, A. C.M.A.J. Vol.110, January 5 (1974)
16. Traumatic Bilateral Renal Artery Thrombosis. Toguri, A., Liu, S.F., Bayliss, C., Amell, F.M. & deVeber, G.A. Journal of Urology, Vol. 112, Oct. (1974)

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Bibliography
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32. Renal Allograft Rejection and Intensive Plasma Exchange. Cardella, C., Sutton, D.M.C., Uldall, P.R., Katz, A. & deVeber, G.A.; Advanced Component Seminar Sponsored by Haemonetics Research Institute. Boston, Mass. March, 1979.
33. Some Observations on the Complications of Intensive Plasma Exchange. Sutton, D.M.C., Cardella, C.J., Uldall, P.R. & deVeber, G.A.; Advanced Components Seminar sponsored by Haemonetics Research Institute. Boston, Mass. March, 1979.
34. A Subclavian Cannula for Temporary Vascular Access for Haemodialysis or Plasmapheresis. Uldall, P.R., Dyck, R.F., Woods, F., Merchant, N., Martin, G.A., Cardella, C.J., Sutton, D. & deVeber, G.A.; Dialysis and Transplantation, 1979;2(10):963-968.
35. The Role of Intensive Plasma Exchange in the Treatment of Renal Allograft Recipients. Cardella, C.J., Sutton, D.M.C., Uldall, P.R., Katz, A. & deVeber, G.A.; Journal of the Japan Society of Blood Transfusion 1979;25(5/6):143-148.
36. A Controlled Trial Evaluating Intensive Plasma Exchange in Renal Transplant Recipients. Cardella, C.J., Sutton, D.M.C., Katz, A., Uldall, P.R., Harding, M., deVeber, G.A., Corey, P.N. & Cook, G.T.; European Dialysis and Transplant Association, Czechoslovakia, June 1980.
37. Effect and Complications of IPE in Renal Transplant Recipients. Cardella, C.J., Uldall, P.R., Sutton, D.M.C., Katz, A., Harding, M., deVeber, G.A. & Cook, G.T.; International Symposium on Plasma Exchange, Germany, 1980.
38. Renal Transplantation in Diabetes Mellitus. Cardella, C.J., Tam, P.Y.W., Walker, J.F., deVeber, G.A. & Cook, G.T.; Peritoneal Dialysis Bulletin (Supplement) 1982;2:S17-S19
39. The Effect of Pre-Transplant Blood Transfusion on Graft Outcome in Patients on Peritoneal Dialysis Prior to Renal Transplantation. Walker, J.F., Oreopoulos, D.G., Uldall, P.R., Cook, G.T., deVeber, G.A. & Cardella, C.J.; Transplantation Proceedings, Vol. XIV (4) December 1982.
40. The Role of Percutaneous Transluminal Dilatation in the Treatment of Transplant Renal Artery Stenosis. Whiteside, C.I., Cardella, C.J., Yeung, H., deVeber, G.A. & Cook, G.T.; Clinical Nephrology 1982;17(2):55-59
41. Wegener's Granulomatosis and the Respiratory System. Lawson, V., Reid, A.J., Cardella, C.J. & deVeber, G.A.; The Journal of Otolaryngology, 1982;11(1):60-64.
42. Renal Transplantation in Patients on Continuous Ambulatory Peritoneal Dialysis. Cardella, C.J., Tam, P.Y.W., Cook, G.T., deVeber, G.A. & Oreopoulos, D.G.; Nefrologia 1982, Vol. II - Supplement.
43. A Clinical Approach to Microscopic Haematuria - Ontario Medicine December 9, 1985. G.A. deVeber, M.D.
44. A Controlled Trial Comparing Sequential Antilymphocyte Sera and Cyclosporine Therapy to Conventional Therapy in Renal Transplant Recipients. Cardella C.J., Harding M.E., deVeber G.A., Honey J., Cook G.T.; Transplant Proc 1987;19:1996-1998
45. The Sensitized Patient: A Single Center Study. Cardella, C.J., Rochon, J., Shoker, A., Harding, M., Falk, J., Jordan, M., deVeber, G., and Cook, G.; Clinical Transplants 1988.

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Bibliography
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46. Successful Treatment of Systemic Blastomycosis With High-Dose Ketoconazole in a Renal Transplant Recipient. Hii, J.H., Legault, L., deVeber, G., Vas, S.I.; American Journal of Kidney Diseases, June 1990;XV(6):595-597
47. Low Dose Cyclosporin from the Early Postoperative Period Yields Potent Immunosuppression after Renal Transplantation. Brady, H., Kamel, K., Harding, M.E., Cook, G.T., deVeber, G.A., Cardella, C.J.; Nephron 1990;55:394-399